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Successful Treatment of Relapsed Infant Acute Lymphoblastic Leukemia With Intensive Antimetabolite-based Chemotherapy

Julio C. Barredo,* Usman Yusuf, Miguel Abboud, and Joseph Laver

Purpose. The treatment of infant acute lymphoblastic leukemia (ALL) continues to be a significant challenge for pediatric oncologists due to the high incidence of early relapses. Salvage regimens used to date have met limited success. We describe two cases of relapsed infant ALL who have achieved long-term survival with an intensive antimetabolite-based salvage regimen.

Patients and Methods. Two consecutive infants with relapsed ALL presented at our institution and were treated with an antimetabolite-based regimen. Both cases exhibited clinical and biological phenotypes previously associated with infantile ALL.

Results. Both patients have achieved prolonged and sustained remissions 48 and 30 months EFS respectively following therapy with intensive antimetabolite-based salvage regimen.

Conclusions. An intensive multiagent antimetabolite-based salvage regimen resulted in prolonged EFS in two cases of relapsed infant ALL. Dose intensification was achieved by administering repeated cycles of the same treatment schema using high dose chemotherapy throughout therapy. These infants were spared prophylactic cranial irradiation without a negative impact on outcome. The use of L-asparaginase, timed after high-dose Cytarabine (ARA-C) throughout therapy, might have contributed to their cure. Med. Pediatr. Oncol. 29: 256–259, 1997.

Key words: acute lymphoblastic leukemia; infant leukemia; chemotherapy; antimetabolites

INTRODUCTION

The prognosis for children with acute lymphoblastic leukemia (ALL) treated with multiagent chemotherapy regimens continues to improve. Recent reports indicate these patients are capable of achieving an average overall long-term event-free survival (EFS) rate of greater than 70% [1,2]. Nevertheless, the outcome for patients in ''high-risk'' groups and for those who relapse while on chemotherapy, continues to be dismal. Among them, infants under twelve months of age continue to be a therapeutic challenge and most survival rates traditionally reported are in the range of 20–30% with front-line chemotherapy [3,4]. Only recently, two trials have reported a higher EFS for infantile ALL with up-front therapy ranging from 45 ± 14% [5] to 55 ± 15% [6], respectively. The explanation for the higher risk for infant ALL is provided by multiple studies published during the last decade indicating that this leukemia has unique clinical and biological characteristics. For instance, the incidence of hyperleukocytosis, hepatosplenomegaly, and central nervous system (CNS) leukemia which are generally associated with a poor prognosis, is higher in this age group. Other significant biological differences have also been identified, like the majority of cases of infant ALL expressing CD10(CALLA)−, CD19+, and HLA-DR+ phenotypes [7]. Finally, a substantial subgroup of infants with ALL have cytogenetic evidence of 11q23 translocations and appear at higher risk for relapse and early treatment failure [8]. These unique features of infant ALL have prompted investigators to use intensive therapies in an attempt to improve long-term survival (EFS). Unfortunately, most strategies implemented to date have met only limited success. We report two consecutive cases of relapsed infant ALL who presented at our institution and have achieved prolonged EFS using an intensive antimetabolite-based chemotherapeutic salvage regimen.

CASE REPORT

Patient 1

A seven-month-old female infant was referred to our institution in June of 1989 due to fever and anemia. Physical exam revealed presence of cervical lymphadenopathy and splenomegaly. An initial CBC showed a WBC 15,000/mm^3, Hb 7.1 gm/dl, platelet count 119,000/mm^3, and presence of ''immature'' lymphoid cells in the peripheral blood. A bone marrow aspirate indicated a

Division of Pediatric Hematology-Oncology, Medical University of South Carolina (MUSC), Charleston, South Carolina.

*Correspondence to: Julio C. Barredo, MUSC Children's Hospital, Charleston, SC 29425.
E-mail: barredjc@musc.edu

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Treatment Schema:

Day	ARA-C	L-Asp	MTX	VCR	PDN	*IT-MTX
1	X	X				X
2			X			
3		X				
4	X					
5		X		X	X	
6					X	
7					X	
8					X	
9					X	
10					X	
11				X	X	

ARA-C	3gm/m^2 IVCD x 3h
L-Asp	6000 U/m^2 IM
MTX	200mg/m^2 IVCD x 4h
VCR	1.5 mg/m^2 (max 2 mg) IV
PDN	180 mg/m^2/d PO x 7d
IT-MTX	Age appropriate dose q 12wk

Each cycle given q 21-28d, when ANC>1000; platelet count>100,000.

Fig. 1. Treatment schema. Abbreviations used are: ARA-C (cytosine arabinoside), L-Asp (L-asparaginase), MTX (methotrexate), VCR (vincristine), PDN (prednisone), IT (intrathecal), IVCD (intravenous continuous drip), IV (intravenous), IM (intramuscular), and PO (oral).

hypercellular specimen infiltrated with over 90% lymphoblasts. Immunophenotype was CD10-, CD19+, and DR+, diagnostic of CALLA negative ALL; with a complex karyotype (47XX,19p+/46XX,−15,19p+/46XX, −16, 19p+) in the blast population. The patient had no evidence of CNS leukemia at the time of diagnosis. She was started on induction chemotherapy with prednisone (PDN), cyclophosphamide (CTX), cytarabine (ARA-C), vincristine (VCR) and triple intrathecal chemotherapy (TIT, methotrexate, hydrocortisone and cytarabine ''c'') After achieving a complete remission, the patient continued intensification treatment with VCR, CTX, ARA-C, etoposide (VP-16), PDN and TIT. All drugs were administered at what are considered conventional doses for the treatment of childhood ALL, following the traditional schema of intensive induction and consolidation, and a subsequent maintenance phase [9]. Six months after the original diagnosis the patient presented with blasts in the peripheral blood, and a bone marrow aspirate confirmed a systemic relapse. Again, there was no evidence of CNS leukemia. Immunophenotype at this time was consistent with CALLA negative ALL. A search for a related or unrelated bone marrow donor failed to identify any suitable candidate. The patient was started on an antimetabolite-based salvage regimen consisting of monthly cycles of Cytarabine (ARA-C), L-asparaginase (L-ASP), MTX, VCR, PDN, and IT-MTX, based on a modification of a regimen previously reported by Steinherz et al [10] (Fig 1). A total of 24 cycles of chemotherapy therapy were administered before discontinuing treatment. To date the patient continues in remission 48 months off chemotherapy, free of any significant treatment-related side-effects.

Patient 2

A four-month-old male infant presented in December 1988 with respiratory distress, fever, and hyperleukocytosis. Physical exam revealed adenopathy and hepatosplenomegaly. An initial CBC showed a WBC 267,000/mm^3, Hb 9.9 gm/dl, platelet count 60,000/mm^3, and presence of leukemic blasts in the peripheral blood. Initial flow cytometry analysis revealed a CD10−, CD19+, DR+ phenotype. Cytogenetic analysis in this blast population was uninformative. CSF examination yielded no evidence of CNS leukemic infiltrate. The diagnosis of CALLA negative ALL was established and remission induction chemotherapy was started using PDN, CTX, ARA-C, VCR, and TIT. Consolidation therapy was given with Cytarabine (ARA-C), teniposide (VM-26), VCR, CTX, PDN, and TIT and maintenance treatment continued with weekly MTX and daily 6-mercaptopurine (6-MP). As was the case for patient 1, all drugs were administered at conventional doses, and these regimens differed only in the substitution of VM-26 for VP-16. A bone marrow aspirate done at the end of therapy on December 1991 showed normal trilineage hematopoiesis without evidence of leukemia.

This patient had an uneventful course until six months later when he presented with testicular enlargement. A

testicular biopsy showed leukemic infiltrate and a bone marrow aspirate confirmed a concurrent systemic relapse. Immunophenotype and cytogenetics at this time were consistent with those at the time of the original diagnosis (CALLA negative ALL). A search for a suitable related or unrelated bone marrow donor yielded negative results. The patient was treated with the same salvage regimen as described for patient 1 (Fig. 1), with the addition of radiation therapy to the testes (1800 cGy). He remains in complete remission 30 months after completing chemotherapy.

DISCUSSION

In general, it has been shown in multiple studies that even though childhood ALL is one of the most curable human neoplasias, treatment failure and mortality for patients after leukemic relapse remains extremely high [10]. In particular, infants with ALL continue to present a significant and unique therapeutic challenge for pediatric oncologists due to its unfavorable biological characteristics, high resistance to chemotherapy, and increased potential for treatment related toxicity. The high proportion of CALLA negative ALL and high incidence of 11q23 translocations denote a particularly aggressive leukemic phenotype in this population [7,8].

The clinical presentation and biological phenotype of the two infants subjects of this report are consistent with those reported for infant ALL. Both patients presented with CALLA (CD10) negative ALL, adenopathy, and organomegaly, and patient 2 had significant hyperleukocytosis. It is noteworthy that in neither case a translocation involving 11q23 was identified, although cytogenetic analysis for patient 2 was uninformative. Nevertheless, the other clinical parameters at presentation were indicative of a high risk leukemic phenotype. In addition, it has been well documented that independent of initial leukemic phenotype, patients with ALL who suffer a systemic relapse have a dismal prognosis [11]. Furthermore, failure of achieving a prolonged EFS in infants with ALL is not due to induction failure but to early relapse [12]. This observation suggests a highly resistant phenotype that is likely expressed at diagnosis by a subpopulation of blasts, or the ability of these blasts to develop drug resistance early after exposure to chemotherapeutic agents.

This reported poor outcome has prompted investigators to consider various strategies aimed at treatment intensification in order to improve survival for infants with ALL. The study by Rivera et al [5] reported a 45 ± 14% EFS for infants with ALL using conventional chemotherapy at diagnosis, even though only 11 patients under 12 months were included in their study. Their treatment strategy was designed around ''reinforced early'' use of rotating, at least partially non-cross-resistant combinations of drugs, which included alkylating agents, epidophyllotoxins, and anthracyclines. Another study has reported a 4-yr 36% EFS for infants with ALL treated with an intensive multiagent chemotherapy [13]. This regimen also included the use of anthracyclines and alkylating agents, and both trials included the use of prophylactic cranial irradiation (1800 cGy). Encouraging results (EFS rate of 55 ± 15%) in 11 infants have been reported by Schorin et al [6] using high dose ARA-C and MTX. The ALL-REZ BFM 85 study, which included some infants, reported an EFS rate of 31 ± 4% for relapsed childhood ALL [14]. Their strategy was also the use of intensive chemotherapy throughout the entire duration of therapy, but unlike our two cases their patients received anthracyclines, epidophyllotoxins, and alkylating agents. Another widely used strategy for treatment intensification in childhood ALL in second or subsequent remission, has been the use of allogeneic or autologous bone marrow transplantation (BMT). Unfortunately, none of the larger series published have included a significant number of infants and the reported survival rates range from 40% (at 2.4–10.4 yr) to 84% (estimated at 5 yr; confidence interval 7.2–29%) [15–17].

The treatment strategy used for the two patients subject of our report differs in several aspects to those previously proposed. Even though the schema used is based on a previously reported regimen by Steinherz et al [10], the overall treatment strategy was not based on the conventional sequence of induction, consolidation, and maintenance chemotherapy frequently used to treat childhood ALL, but rather on repeating cycles of intensive therapy throughout the 24-month treatment period. Our approach also differs from that of the ALL-REZ BFM 85 [14] regimen in that our patients did not receive any anthracylines, epidophyllotoxins, alkylating agents, or cranial irradiation. Thus dose intensity was achieved by using higher than conventional doses of effective drug combinations less likely to result in late sequelae, and by exposure to higher drug dosages throughout the entire 24-month duration of therapy. Nevertheless, this intensive regimen can be administered almost entirely on an outpatient basis contributing to a better quality of life and significantly reducing treatment costs. It is also noteworthy that this regimen is based mainly on the use of antimetabolites, a class of drugs less likely to result in secondary malignancies and other undue long-term side-effects in young children. Further, neither of our two patients received prophylactic CNS irradiation, decreasing the possibility of long-term neuro-psychological sequelae in these infants. Finally, this salvage regimen differed from the up-front treatment, in that it included the use of the of L-asparaginase throughout the entire 24 cycles administered. A recent report from Abshire et al indicated a significant remission induction advantage for patients with relapsed ALL receiving conventional

PVDA (PDN, VCR, doxorubicin, and L-asparaginase) induction with more intensive asparaginase dosing in the form of polyethylene glycol conjugated (PEG) L-asparaginase [18]. Furthermore, in our patients L-asparaginase was always administered following high-dose Cytarabine (ARA-C), a known effective drug combination for the treatment of refractory ALL that could have potentially contributed significantly to their cure [19].

In conclusion, we have reported the successful treatment of relapsed infantile ALL in two consecutive patients using an intensive antimetabolite-based regimen. Our results suggest this regimen could prove to be an effective treatment for infants with ALL who do not have cytogenetic risk factors, or as rescue therapy for other children with relapsed B-lineage ALL.

ADDENDUM

Since the initial submission of this manuscript the two patients in this report have continued to be in complete remission 54 and 36 months off chemotherapy, and are free of any significant therapy induced long-term side-effects.

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